REMARKS

Claims 1, 13, 18, 57, 61, 87-88, 103, 112, 130, 149, and 158-206, are pending in this application upon entry of this amendment. Reconsideration and allowance of all claims are respectfully requested in view of the following remarks.

Examiner Interview

The Applicants thank the Examiner for the courtesies extended during the telephone interview of September 12, 2008. No agreement was reached; however, the Applicants appreciate the Examiner's explanation of the Office Action and thank the Examiner for her responsiveness to the Applicants position on the interpretation of the claims and prior art.

Withdrawal of Allowed Claims

The Examiner has withdrawn the allowance of Claims 57 and 61 in view of the newly applied reference Grier et al., USP 6,416,190.

The Applicants respectfully point out to the Examiner that Grier et al., both USP 6,416,190 and 6,055,106, have been applied by the Examiner in the previous Office Action.

112 Rejections

The Examiner has rejected Claims 187-189, 191, 193-197, and 200-202, for lack of antecedent basis.

The Applicants respectfully point out to the Examiner that Claims 193-197 and 200-202, do not lack antecedent basis, since "a phase patterning optical element" is introduced in Claim 88, from which those claims depend. Thus, the rejection should be withdrawn.

With respect to Claims 187-189, and 191, these claims have been canceled without prejudice or disclaimer.

Claim Rejections

Claims 177-180, 182-183, and 185-186, are rejected under 35 U.S.C. §103 as being unpatentable over Grier et al. (USP 6,416,190) (hereafter Grier '190) as applied to Claims 1, 13, 18, 57, 61, 87-88, 112, 159, 162-164, 166, 170, 175-176, 181, 184, 187-189, and 191-206, and further in view of Shivashankar et al. (USP 6,139,831).

Claims 177-180, 182-183, and 185-186, are rejected under 35 U.S.C. §103 as being unpatentable over Grier et al. (USP 6,055,106) (hereafter Grier '106) in view of Ulmer (USP 5,776,674), and further in view of Visscher et al. (IEEE Journal), as applied to Claims 1, 13, 18, 57, 61, 87-88, 112, 158-176, 181, 184 and 187-206, and further in view of Shivashankar et al.

Claims 1, 13, 18, 57, 61, 87-88, 112, 159, 162-164, 166, 170, 175-176, 181, 184, 187-189, and 191-206, are rejected under 35 U.S.C. 102(e) as being anticipated by Grier '190.

Claims 1, 13-18 (*sic*, the Examiner means 13 and 18), 57, 61, 87-88, 112, 158-176, 181, 184, and 187-206, are rejected under 35 U.S.C. 103 as being obvious over Grier '106 in view of Ulmer, and further in view of Visscher et al.

For the following reasons, the prior art rejections are respectfully traversed.

With respect to the rejection of amended Claims 1, 57, 87, and 88, as being anticipated by Grier '190, the Applicants respectfully submit that Grier '190 does not teach or suggest a method of configuring and tracking an array of probes including sorting and selecting at least two of the probes for inclusion in an array of probes contained within the optical traps based on predetermined binding and reactivity characteristics of the probes; trapping each of the selected probes having said predetermined binding and reactivity characteristics with a corresponding one of the optical traps to configure the array of probes contained within the optical traps; and, tracking a position of at least one of the trapped probes in the array by computerized monitoring of the position of the optical trap which contains it, as substantially recited in Claims 1, 57, 87, and 88; nor introducing into the vessel at least one target comprised of a

biological material; and determining the reaction or lack thereof, of each of the trapped probes with each of the targets; wherein the probes which react with the targets are segregated from the remaining probes, as further recited in Claim 57.

Grier '190 discloses a method and apparatus of using optical tweezers to control optical trap arrays in three dimensions, using computer generated holograms. Grier '190 further includes an adaptive tweezer mode where a movable knife edge is moved into the path of several laser beams, selectively blocking the laser beams to prevent formation of a portion of the optical traps. Filling of the optical traps with different types of particles can also be performed using such preferential blocking methods. Various devices are provided to accelerate filling of the optical traps.

However, Grier '190 does not teach or suggest sorting and selecting at least two probes for inclusion in the array based on predetermined binding and reactivity characteristics of the probes, trapping those selected probes with a corresponding optical trap, and tracking a position of at least one of the trapped probes in the array by computerized monitoring of the position of the optical trap which contains it. Further, there is no segregation of particles which react with targets, disclosed or taught by Grier '190.

Rather, Grier '190 is silent with respect to these features. Grier '190 fails to disclose any method of sorting and selection of the type of particles based on any predetermined characteristics of those particles. Further, Grier '190 do not disclose or suggest computerized tracking of any preselected particles by tracking their corresponding optical traps.

Further, the Examiner misunderstands the adaptive tweezer mode and the movable knife edge in Grier '190. The knife edge simply blocks beams of light from forming optical traps, such that the optical traps are formed in a controlled way, and the particles fill the optical traps in a predetermined format. This is not related to computerized tracking of the optical traps containing preselected probes, as in the present invention.

Accordingly, Claims 1, 57, 87, and 88, are not anticipated by Grier '190, and the rejection of Claims 1, 57, 87, and 88, under 35 USC 102(e), should be withdrawn.

Further, with respect to Claims 163-164, 166, and 170, the Applicants respectfully submit that Grier '190 does not teach or suggest a method of assaying biological material wherein the movement of each optical trap is controlled by a computer, as recited in Claim 163; nor receiving the optical data-stream with a computer, as recited in Claim 164; nor analyzing the optical data stream with the computer, as recited in Claim 165; nor using the computer to direct the movement of one or more optical traps based on the analysis of the optical data stream, as recited in Claim 166; nor using the computer to direct the movement of one or more optical traps based on the analysis of the video signal, as recited in Claim 170.

Grier '190 is silent with respect to these features. Again, the Examiner has misunderstood controlling of the diffractive optical element using a computer, to produce holograms, in Grier '190, with the control of the optical traps by a computer 38 (see Fig. 3B), where the optical data stream 32 (including a video signal) is monitored and analyzed in order to control movement of the optical traps. Grier '190 is silent with respect to any computer control of the optical traps or of analyzing an optical data stream.

Accordingly, Claims 163-164, 166, and 170, are not anticipated by Grier '190, and the rejection of Claims 163-164, 166, and 170, under 35 U.S.C. 102(e) should be withdrawn.

With respect to amended Claim 176, the Applicants respectfully submit that Grier '190 does not teach or suggest a method of assaying biological material wherein at least two of the probes have binding or reactivity characteristics that differ from one another and at least one of the probes is sorted and selected by segregating the probe based on its different binding or reactivity characteristic by moving the probe to a predetermined location within the vessel and using the location of the segregated probe to select the probe. Further, the Grier '190 fail to disclose or suggest that the predetermined location is one of a physical sub-cell or an optical sub-cell, as recited in Claim 181. Still further, Grier '190 fail to

disclose or suggest that the probes are segregated using movement by optical traps, flow channels or micro-capillaries, as recited in Claims 192 and 206.

Rather, Grier '190 is completely silent with respect to these features. The particles in Grier '190 are not sorted and selected by segregating them based on their different binding or reactivity characteristics, nor by moving the particles to a predetermined location in a vessel, or using a location (physical or optical sub-cell) of a segregated particle to select the particle. Grier '190 discloses forming arrays of particles without any of the claimed limitations.

Accordingly, Claims 176, 181,192, and 206, are not anticipated by Grier '190, and the rejection of Claim 176, 181, 192, and 206, under 35 U.S.C. 102(e) should be withdrawn.

With respect to Claims 194-197, the Applicants respectfully submit that Grier '190 does not teach or suggest a method of configuring or reconfiguring an array of probes wherein the static surface is comprised of two or more discrete regions, as recited in Claim 194; wherein the position of at least one of the probes contained within the optical traps is altered by changing the discrete region of the static surface to which the beam of light is directed, as recited in Claim 195; wherein the static surface is substantially continuously varying, as recited in Claim 196; wherein the position of the at least one optical trap is altered by changing the region of the static surface to which the beam of light is directed, as recited in Claim 197; nor wherein the phase patterning optical element has a discrete static surface, and wherein a form of at least one of the optical traps is changed by moving the discrete static surface, as recited in Claim 203.

Although Grier '190 disclose a diffractive optical element with a static surface, the ability to move the discrete static surface, or have two or more discrete regions in the static surface, and these discrete regions being able to be changed, and thus, altering the position of the probes or the optical traps thereby, are not taught or suggested by Grier '190. However, by having such a movable discrete static

surface, or discrete regions in a static surface, better control can be afforded in directing the beam of light and thus, moving the position of the probes and optical traps.

Accordingly, Claims 194-197 are not anticipated by Grier '190, and the rejection of Claims 194-197, under 35 U.S.C. 102(e) should be withdrawn.

Finally, since Claims 13, 18, and 112, depend from Claim 1, Claims 61, 159, 162-164, 166, 170, 175-176, 181, 184, 187-189, and 191-192, depend from Claim 57, and Claims 193-206, depend from Claim 88, they are also patentable over the applied prior art by virtue of their respective dependency from Claims 1, 57, and 88.

With respect to the rejection of Claims 1, 57, 87, and 88, as being obvious over Grier '106, Ulmer, and Visscher et al., the Applicants respectfully submit that neither the individual nor the combination of these references teaches or suggests a method of configuring and tracking an array of probes including sorting and selecting at least two of the probes for inclusion in an array of probes contained within the optical traps based on predetermined binding and reactivity characteristics of the probes; trapping each of the selected probes having said predetermined binding and reactivity characteristics with a corresponding one of the optical traps to configure the array of probes contained within the optical traps; and, tracking a position of at least one of the trapped probes in the array by computerized monitoring of the position of the optical trap which contains it, as recited in Claims 1, 57, 87, and 88; nor introducing into the vessel at least one target comprised of a biological material; and determining the reaction or lack thereof, of each of the trapped probes with each of the targets; wherein the probes which react with the targets are segregated from the remaining probes, as further recited in Claim 57.

Grier '106 discloses an apparatus for manipulating particles by forming optical traps, including a diffractive optical element, and a focusing element, wherein multiple light beams are used to create multiple holographic optical traps and create arrays in three dimensions. Continuous translation of an

entire array as a unit, can be performed, where the array is translated vertically relative to a sample stage by moving the sample stage or by adjusting a telescope, or laterally by moving the sample stage.

First, the Applicants respectfully point out to the Examiner, that Grier '106 precedes Grier '190, and thus, is directed simply to creating holographic optical traps. As stated above with Grier '190, Grier '106 does not teach or suggest sorting and selecting at least two probes for inclusion in an array based on predetermined binding and reactivity characteristics of the probes, trapping those selected probes with a corresponding optical trap, and tracking a position of at least one of the trapped probes in the array by computerized monitoring of the position of the optical trap which contains it.

Rather, Grier '106 is silent with respect to these features. Grier '106 fails to disclose any method of sorting and selection of the type of particles based on any predetermined characteristics of those particles. Further, Grier '106 do not disclose or suggest computerized tracking of any preselected particles (based on their predetermined characteristics) by tracking their corresponding optical traps. Further, there is no segregation of particles which react with targets, disclosed or taught by Grier '106.

Ulmer discloses an optical trap which is used to translate a particle through a thin film coating on an optically flat surface. Ulmer discloses optically trapping a particle in one region of a heterogeneous thin liquid film coating, and moving the particle through a series of droplets deposited in the thin film coating, where each droplet contains a different chemical or biochemical or biological agent, such that the last droplet produces a desired product.

Contrary to the present invention, Ulmer discloses only trapping one particle-coupled probe which is then moved from a first droplet 112 through the thin film 110 into the second droplet 114 – in two dimensions. There is no array formed. The resulting complex is then moved by the optical trap through thin film 110, to another droplet 116 where it is collected and manipulated (see col. 7, lines 28-44).

However, in the present invention, multiple traps are created which are independently movable in a vessel - i.e., in three dimensions, not two dimensions as in Ulmer. In addition, since there is no array formed, there are no tracking, or sorting functions performed, since only single particles/probes are involved. Further, the particles/probes are not selected due to any particular binding or reactivity characteristics, but rather, they undergo certain chemical and biochemical reactions from start to finish, to produce a certain product or result.

Further, the computer 400 used in Ulmer is not for monitoring the position of the optical trap which contains the probe – rather, it is for storing information on the fluorescent photon events, and identifying the nucleotides (see col. 10, lines 46-61, and col. 12, lines 14-17). Still further, Ulmer only disclose viewing of the probes by human observation. Since the individual probes in the array are not movable without moving the array itself (i.e., the tweezer array is translatable only as a unit by various means - see col. 5, lines 38-39, and 45-49), computerized tracking of any individual probe in the array is not possible.

Visscher et al. disclose two different types of multiple-beam optical tweezers, where three-dimensional trapping of objects in water, has been demonstrated. The methods described predict the stiffness of an optical trap, including the force required to pull an object free from the trap, including an escape force method, a drag force method, an equipartition method, a power spectrum method, and a step response method. Visscher et al. disclose scanning a laser beam among a set of positions quickly enough to mimic the effect of steady illumination. In a multiple-beam trap, line traps were created, where scanning rates were chosen to achieve time-shared traps.

Visscher et al. is completely silent with respect to configuring and tracking an array of probes including sorting and selecting at least two of the probes for inclusion in an array of probes contained within the optical traps based on predetermined binding and reactivity characteristics of the probes; trapping each of the selected probes having said predetermined binding and reactivity characteristics with

a corresponding one of the optical traps to configure the array of probes contained within the optical traps; and, tracking a position of at least one of the trapped probes in the array by computerized monitoring of the position of the optical trap which contains it, as recited in Claims 1, 57, 87, and 88; nor introducing into the vessel at least one target comprised of a biological material; and determining the reaction or lack thereof, of each of the trapped probes with each of the targets; wherein the probes which react with the targets are segregated from the remaining probes, as further recited in Claim 57.

Contrary to the Examiner's assertion, Visscher et al. fail to disclose any computerized tracking of any individual optical traps, since Visscher et al. disclose that the method is relatively "insensitive" to the absolute location of a trapped particle within the field of view (see Visscher et al., Abstract). Rather, Visscher et al. only disclose the stiffness of an optical trap, and any reference to multiple traps states that the traps are not independently movable. Instead, the traps are time-shared traps which are accomplished through a high scanning rate of a laser beam to appear as if there is steady illumination.

Further, there is no motivation to combine Grier '106, Ulmer and Visscher et al., since each of these references are complete in themselves, and one of ordinary skill in the art would not be motivated to combine Grier '106, Ulmer and Visscher et al. without impermissible hindsight.

For example, the apparatus and methods of Grier '106 – in creating holographic optical traps – would not be useful in Ulmer, since Ulmer is directed to creating a specific product by having a particle undergo specific chemical and biochemical reactions. Further, determining the optical stiffness of an optical trap, as in Visscher et al., is not useful in Grier '106, or Ulmer. Thus, modification of these references, either singly, or in combination, nor their combination, would not reach the claimed features of the present invention.

The Examiner is reminded that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See MPEP §2143) The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Since there is no suggestion or motivation, either in Grier '106, Ulmer, or Visscher et al., or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings, the Examiner has failed to establish a *prima facie* case of obviousness. Further, since the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Furthermore, the Examiner is reminded that "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) cited with approval in *KSR Int'l v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007)).

Accordingly, Claims 1, 57, 87, and 88, are not obvious over either the individual or the combination of the Grier '106, Ulmer and Visscher et al. references, and the rejection of Claims 1, 57, 87, and 88, under 35 U.S.C. 103, should be withdrawn.

With respect to Claims 160, and 163-174, the Applicants respectfully submit that neither the individual nor the combination of Grier '106, Ulmer, and Visscher et al. teaches or suggests producing an optical data stream of data corresponding to the identity and position of at least one of the optical traps, as recited in Claim 160; nor wherein the movement of each optical trap is controlled by a computer, as recited in Claim 163; nor receiving the optical data-stream with a computer, as recited in Claim 164; nor

analyzing the optical data stream with the computer, as recited in Claim 165; nor using the computer to direct the movement of one or more optical traps based on the analysis of the optical data stream, as recited in Claim 166; nor converting the optical data-stream to a video signal; as recited in Claim 167; nor receiving the video signal with a computer, as recited in Claim 168; nor analyzing the video signal with the computer, as recited in Claim 169; nor using the computer to direct the movement of one or more optical traps based on the analysis of the video signal, as recited in Claim 170; nor wherein the video signal is used to produce an image, as recited in Claim 171; nor viewing the image and directing the movement of one or more of the optical traps based on the viewing of the image, as recited in Claim 172; nor wherein the data is spectroscopic data, as recited in Claim 173; nor using a computer to direct the movement of one or more optical traps based on an analysis of the spectroscopic data, as recited in Claim 174.

The Examiner points to Grier '106 as disclosing these features. However, as stated above, Grier '106 is silent with respect to these features, and the Examiner has misunderstood controlling the diffractive optical element using a computer to produce holograms, in Grier '106, with the control of the optical traps by a computer 38 (see Fig. 3B), where the optical data stream 32 (including a video signal) is monitored and analyzed in order to control movement of the optical traps. Grier '106 is silent with respect to any computer control of the optical traps or of analyzing an optical data stream, where the data is spectroscopic data.

Further, with respect to Claim 176, the Applicants respectfully submit that neither Grier '106, Ulmer, nor Visscher et al., alone or in combination, teaches or suggests a method of assaying biological material wherein at least two of the probes have binding or reactivity characteristics that differ from one another and at least one of the probes is sorted and selected by segregating the probe based on its different binding or reactivity characteristic by moving the probe to a predetermined location within the vessel and using the location of the segregated probe to select the probe. Further, the applied prior art fails to

disclose or suggest that the predetermined location is one of a physical sub-cell or an optical sub-cell, as recited in Claim 181. Still further, the applied prior art fails to disclose or suggest that the probes are segregated using movement by optical traps, flow channels or micro-capillaries, as recited in Claims 192 and 205.

Still further, the applied prior art, alone or in combination, does not teach or suggest a method wherein at least one of the probes is one of bound to a substrate or unbound to a substrate, as recited in Claim 177, or at where at least some probes are bound to a substrate and at least some probes are unbound to a substrate as stated in Claim 185, wherein all the substrate bound probes having the same binding or reactivity characteristic are labeled with the same markers, as recited in Claim 178; nor wherein at least one of the markers is a wavelength specific dye as recited in Claim 179; nor wherein at least one of the substrate bound probes is selected by measuring the spectral response of the wavelength specific dye and using the spectral measurement to select the at least one probe, as recited in Claim 180; nor wherein at least one of the probes is bound to a substrate labeled with a wavelength specific marker and the at least one bound probe is selected by spectroscopically measuring the marker and using the spectroscopic measurement to select the at least one probe, as recited in Claim 182.

As stated above, Grier '106 do not teach or suggest forming arrays based on predetermined characteristics of the probes, where some of the probes or bound or unbound to a substrate. Further, in Ulmer, the probes are not bound to a substrate, nor are they in Visscher et al. Further, the particular predetermined characteristics being markers, such as a wavelength specific dye, or a spectral response to a particular marker, are not disclosed or taught by any of the prior art references.

Further, none of the prior art references teach or suggest moving at least one of the trapped probes by transferring the probe from one optical trap to another, as recited in Claim 185, nor moving at least three of the trapped probes by transferring the probe from a first set of optical traps to a second set of optical traps, as recited in Claim 186.

In addition, the applied prior art references do not teach or suggest a method of configuring or reconfiguring an array of probes wherein the static surface of the phase patterning optical element is comprised of two or more discrete regions, as recited in Claim 194; wherein the position of at least one of the probes contained within the optical traps is altered by changing the discrete region of the static surface to which the beam of light is directed, as recited in Claim 195; wherein the static surface is substantially continuously varying, as recited in Claim 196; wherein the position of the at least one optical trap is altered by changing the region of the static surface to which the beam of light is directed, as recited in Claim 197; nor wherein the phase patterning optical element has a discrete static surface, and wherein a form of at least one of the optical traps is changed by moving the discrete static surface, as recited in Claim 203.

As stated above, although Grier '106 – on whom the Examiner relies - discloses a diffractive optical element with a static surface, the ability to move the discrete static surface, or have two or more discrete regions in the static surface, and these discrete regions being able to be changed, and thus, altering the position of the probes or the optical traps thereby, are not taught or suggested by Grier '106. However, by having such a movable discrete static surface, or discrete regions in a static surface, as disclosed in the present invention, better control can be afforded in directing the beam of light and thus, moving the position of the probes and optical traps.

Further, since Claims 13, 18, and 112 depend from Claim 1, Claims 61, 158-176, 181, 184, and 187-192, depend from Claim 57, and Claims 193-206, depend from Claim 88, they are also patentable over the applied prior art by virtue of their dependency from Claims 1, 57, and 88.

With respect to the rejection of Claims 177-180, 182-183, and 185-186, over either Grier '190, or over the combination of Grier '106, Ulmer, and Visscher et al, the Applicants respectfully submit that the addition of Shivashankar does not make up for the deficiencies in the applied prior art.

Shivashankar et al. disclose an apparatus and method for immobilizing molecules on a substrate. In this reference, a substrate is coated with a colloidal dispersion including insoluble particles coated with a molecule, which are then impinged with a laser beam to form patterns of melting and ablation on the substrate to which the insoluble particles are adhered and immobilized. Although in one embodiment an optical tweezers is used, it is used simply to emit the laser beam such that the beam impinges on the substrate, heats it, and then, the optical tweezer can move the selected particle to the area of impingement to immobilize the particle.

However, none of the applied prior art references, alone or in combination, teaches or suggests wherein all the substrate bound probes having the same binding or reactivity characteristic are labeled with the same markers, as recited in Claim 178, nor wherein at least one of the probes is bound to a substrate labeled with a wavelength specific marker and the at least one bound probe is selected by spectroscopically measuring the marker and using the spectroscopic measurement to select the at least one probe, as recited in Claim 182; nor further comprising moving at least one of the trapped probes by transferring the probe from one optical trap to another, as recited in Claim 183; nor moving at least three of the trapped probes by transferring the probe from a first set of optical traps to a second set of optical traps, as recited in Claim 185.

Rather, Shivashankar et al. – on whom the Examiner relies - are silent with respect to these features. In fact, the Examiner misunderstands the Shivashankar et a l. reference, which only discloses that a molecule coated particle can be exposed to a fluorescently labeled complementary sequences for detection. However, using the spectroscopical measurement of the marker to select a particular probe, is not taught or suggested by Shivashankar et al. Further, there is no disclosure of moving probes from one (set of) trap(s) to another.

Further, there is no motivation to combine Shivashankar et al. with Grier '106, Ulmer, Visscher et al., or Grier '190, since again, this reference is complete in itself, and directed to immobilizing molecules

on a substrate. Certainly immobilizing particles in Grier '190, Grier '106, Ulmer, and Visscher et al., are not desired and would not meet the claimed features of the present invention.

Accordingly, Claims 178, 179, 181-183, and 185 are patentable over the applied prior art.

Further, since Claims 177-180, 182-183, and 185-186, depend from Claim 57, they are also patentably distinguishable over the applied prior art for the reasons cited above with respect to Claim 57.

If the Examiner believes that there is any issue which could be resolved by a telephone or personal interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case, and any required fee for such an extension is to be charged to Deposit Account No. 50-0951.

Respectfully submitted,

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